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Review article – *Special issue: Acute Coronary Syndromes*

Radionuclide imaging in acute coronary syndromes

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ABSTRACT

Introduction: Acute coronary syndrome encompasses acute forms of ischemic heart disease – unstable angina and myocardial infarction with or without ST elevation. Chest pain patients have a wide spectrum of cardiac risk including those with typical symptoms and abnormal electrocardiography who require immediate catheter angiography with a view to intervention; at the other end of the spectrum are those of low risk with atypical symptoms and a normal ECG who can be discharged without investigation. Between these two groups is a large number of patients with diagnostic uncertainty.

Methods: Radionuclide imaging can be useful in different phases of the course of atherosclerosis with subsequent myocardial ischemia. Primarily, radionuclide imaging can be used for the identification of subclinical coronary artery atherosclerosis to enhance primary prevention of CAD, acute myocardial infarction, and sudden cardiac death. Secondly it can be used at the emergency department to help to decide whether to admit or discharge a patient presenting with chest pain. And finally it helps to stratify and follow patients who survive ACS for choosing optimal treatment strategy.

Results: Radionuclide imaging is potentially able to detect endothelial dysfunction and early, preclinical atherosclerotic plaques vulnerable to rupture. Rest ^{99m}Tc-sestamibi SPECT has been shown to improve medical decision making by decreasing unnecessary hospitalizations. The strength of resting MPI lies with its high negative predictive value, approaching 100%. A possible future approach for risk stratification of patients with suspected ACS involves imaging myocardial fatty acid metabolism. The study of myocardial perfusion and metabolism in the sub-acute phase of STEMI has allowed us to considerably improve our knowledge of its pathophysiology, but its clinical usefulness is limited by the complex interplay between epicardial artery obstruction, coronary microvascular obstruction, and inflammatory cell activation.

Conclusion: The optimal imaging strategy in acute coronary syndromes is determined not only by the diagnostic performance of a modality but also by local practice, expertise with imaging techniques, medical facilities, and individual patient characteristics.

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Contents

Introduction

The entity acute coronary syndrome (ACS) encompasses acute forms of ischemic heart disease (IHD) – unstable angina and myocardial infarction (MI) with or without ST elevation [1]. Patients with ACS frequently present with acute chest pain complaints. Chest pain may be cardiac related or may be due to non-cardiac causes such as musculoskeletal or gastrointestinal pain; thus, acute chest pain is a common diagnostic dilemma in the emergency department and its impact on the health care system is substantial. It is important to identify those patients with ischemic heart disease presenting with chest pain [2]. Chest pain patients have a wide spectrum of cardiac risk including those with typical symptoms and abnormal electrocardiography (ECG) who require immediate catheter angiography with a view to intervention; at the other end of the spectrum are those of low risk with atypical symptoms and a normal ECG who can be discharged without investigation. Unfortunately, between these two groups is a large number of patients with diagnostic uncertainty [3]. The results of a large multicenter study showed that although most patients (>60%) with suspected ACS were hospitalized for further evaluation, only 17–20% were ultimately diagnosed with ACS. Despite this conservative approach, a small proportion of patients (0.4–10%) with ACS are misdiagnosed and discharged without appropriate intervention with double the risk-adjusted mortality of admitted patients [1,3–6]. Patients with ACS who are mistakenly discharged from the emergency department generally have a worse prognosis than appropriately managed patients, partly not only because of their risk for sudden cardiac death, but also because of the delay in implementing treatments that are known to be beneficial for ACS [1].

Coronary artery disease (CAD) is the development of cholesterol-rich plaques within the walls of coronary arteries (atherosclerosis). At any stage in the development of atherosclerosis, and often when the coronary artery lumen is narrowed only slightly or not at all, an unstable plaque may develop a tear of its inner lining cell layer, exposing the underlying cholesterol-rich atheroma to the vessel lumen. This atheroma is extremely thrombogenic and initiates platelet aggregation and thrombus formation. Clinical consequence of such a situation is ACS. Depending on the degree of occlusion of the vessel lumen, time duration of the thrombus (spontaneous thrombolysis), collateralization from other vessels and conditioning of the myocardium to ischemia cell death with subsequent necrosis can or cannot occur [3]. Patients with ACS can die, can develop congestive heart failure or can survive without clinical impairment depending on the extent of myocardial necrosis.

Another important consideration is the presence of coincidental CAD. The prevalence of asymptomatic non-obstructive CAD is high, especially in the elderly population. This disease may not be the cause of the patient's pain and it is important not to ascribe the pain to being cardiac just because of the presence of CAD. Confirmatory evidence must be sought so as to not ''convert'' an individual with non-cardiac chest pain and coincidental CAD into a cardiac patient [3].

Radionuclide imaging can be useful in different phases of the course of atherosclerosis with subsequent myocardial ischemia. I would like to divide its use into three groups. Primarily, radionuclide imaging can be used for identification of subclinical coronary artery atherosclerosis to enhance primary prevention of CAD, acute myocardial infarction, and sudden cardiac death [6]. It is potentially able to detect endothelial dysfunction and early, preclinical atherosclerotic plaques vulnerable to rupture. Secondly it can be used at the emergency department to help to decide whether to admit or discharge a patient presenting with chest pain. And finally it helps to stratify and follow patients who survive ACS for choosing optimal treatment strategy [7].

Radionuclide imaging in primary prevention

The term vulnerable plaque has been introduced indicating the high risk of plaque rupture or erosion, which subsequently leads to ACS. The vulnerable plaque is, however, difficult to detect, and no biomarkers have been identified so far to allow for early detection of the disease [8]. Sites of atherothrombosis leading to ACS are associated with plaque rupture (60%), plaque erosion (30%), calcified nodules (2–7%) or very rarely with isolated intra-plaque hemorrhage. Plaque rupture has been initially considered predominantly mechanical, as it occurs at sites of turbulent blood flow. Very soon several distinct biological features of rupturing plaques became apparent. They are characterized by the presence of a thin fibrous cap, overlying a necrotic core which is heavily infiltrated by macrophages (density up to 26%) and T lymphocytes. While a morphological assessment of atherosclerotic plaques provides limited information in predicting ACS, a functional assessment of inflammatory cells within the plaque might better serve this scope. In particular, molecular imaging of inflammatory cells within the plaque might help to

identify vulnerable plaques prone to become unstable, irrespective of their severity and morphology [9].

Radionuclide imaging techniques including SPECT and PET hold the potential for superior functional and molecular atherosclerotic imaging for prediction of the risk of plaque rupture. These techniques allow the study of changes at a cellular and molecular level, and have been used for clinical and research purposes to study myocardial perfusion, innervation, angiogenesis, gene expression and stem cell labeling. While such metabolic information is surplus to that provided by MRI and MDCT, scintigraphic imaging techniques are limited by relatively poor spatial and temporal resolution [10].

There are several targets that can be used to detect vulnerable plaque.

Glucose is the most important substrate for metabolically active cells, so its analog fluorodeoxyglucose labeled with Fluorine-18 (^{18}F-FDG) was suggested to accumulate within the atherosclerotic plaque in proportion to the degree of inflammation and macrophage density. Rudd et al. demonstrated that human carotid plaque inflammation can be imaged with ^{18}F-FDG PET and that symptomatic plaques accumulate more ^{18}FDG than asymptomatic lesions [11]. In addition, histological examination of the excised symptomatic plaques in this study revealed heavy macrophage infiltration. The assessment of plaque inflammation by ^{18}F-FDG in coronary arteries is more challenging than that in carotid arteries for several reasons. First, PET imaging has a limited spatial resolution (3–4 mm), thus mandating the use of concomitant structural imaging (either computed tomography or magnetic resonance imaging) to guide localization of the ^{18}F-FDG signal. Secondly, coronary ^{18}F-FDG imaging is challenged by its uptake in adjacent myocardium, a hurdle that can be partially overcome by the administration of FFA-enriched and low-carbohydrate meals to suppress myocardial glucose metabolism [9]. Nevertheless Rogers et al. demonstrated increased ^{18}F-FDG accumulation both within the culprit lesion and in the ascending aorta and left main coronary artery [12].

Calcification is another key feature of human atherosclerosis. Coronary artery calcium scoring provides a surrogate measure of the atherosclerotic burden and is a powerful predictor of cardiovascular risk. Risk prediction can be improved by examining the progression of coronary calcification and by detecting spotty calcification [13]. Fluorine-18 sodium fluoride (^{18}F-NaF) is incorporated directly into exposed hydroxyapatite crystal via an exchange mechanism with hydroxyl groups. Therefore it detects novel areas of calcification as its uptake reflects active calcification of atherosclerotic plaque. Therefore, ^{18}F-NaF seems to distinguish between patients with dormant calcific disease, established many months or years previously, and subjects with metabolically active disease where the calcification process is ongoing. Importantly this distinction seems to be of clinical relevance, with higher rates of anginal symptoms, prior MACE events, and cardiovascular risk factor scores observed in those with active disease. The spatial resolution of PET/CT is sufficient to localize ^{18}F-NaF activity to specific coronary territories, suggesting that ^{18}F-NaF might be able to identify the presence and location of recent plaque rupture. But still much research needs to be done before the technique can become a viable clinical option [14].

Radionuclide imaging of patients with acute chest pain in the intensive care unit

Clinical evaluation is fundamental to diagnosis, risk stratification and decision making in patients with chest pain and suspected ACS. A detailed history remains the cornerstone of the evaluation of patients with suspected ischemic coronary syndromes. A diagnosis of ACS can be made based solely on history if there is a compelling clinical scenario in a patient with a moderate or high probability of ACS. However, the majority of patients require further evaluation [3]. Risk stratification into categories defined by the American College of Cardiology/American Heart Association criteria should be performed as indicated by the history, physical examination, ECG, and cardiac injury markers. Low-risk patients for ACS are those with no hemodynamic derangements or arrhythmias, a normal or near-normal ECG, and negative initial cardiac injury markers (mainly Troponin), which correlate with low likelihood of ACS [15]. In such patients a confirmatory test is performed by any of several methods, from exercise treadmill testing to cardiac imaging, depending on the specific features of each patient. Negative results further minimize the probability of ACS, thereby optimizing the safety and rationale of discharging these patients.

Myocardial perfusion imaging (MPI) using SPECT has been evaluated in several publications as an effective tool within a chest pain work-up algorithm. Among patients presenting to the emergency department with chest pain, nondiagnostic ECG, and normal initial serum markers and enzymes, myocardial perfusion SPECT has been shown to have a high negative predictive value to rule out myocardial infarction (99%) or future adverse cardiac events (97%) [6]. Moreover, rest ^{99m}Tc-sestamibi SPECT has been shown to improve medical decision making by decreasing unnecessary hospitalizations or prolonged observation periods in the emergency department. In the context of acute chest pain (<6 h), its sensitivity for detecting myocardial infarction is high (approximately 92%; range, 90–100%) [3]. However, the specificity of rest imaging is suboptimal (67–78%) and has positive predictive values of only 43–45%. One of the main reasons for this is that hypoperfusion can be due to chronic ischemia, artifacts or unstable angina without myocardial necrosis. Thus, abnormal MPI is not specific for ongoing ACS. In a trial of 2475 patients who presented with chest pain, randomization to a strategy with acute rest MPI did not affect triage decisions in those patients in whom the eventual diagnosis was myocardial infarction or unstable angina; however, among those patients without acute coronary ischemia (85% of the patients), MPI did reduce the rate of admission [16]. The strength of resting MPI lies with its high negative predictive value (approaching 100%) and its value in short-term risk stratification. Patients with a normal rest MPI have a very low (<1%) 30-day cardiac event rate, whereas patients with abnormal rest MPI may have a 10–20% 30-day cardiac event rate. Also Peix et al. confirmed that patients presenting with acute chest pain and a low-to-intermediate likelihood of coronary artery disease with a normal rest MPI have a very low probability of cardiac events during the first year of follow-up. Coronary calcium score was not helpful in risk-stratifying these patients [17]. However, the

timing of rest MPI is crucial. Optimal timing is during pain, and certainly no longer than 6 h following relief of pain. Thus, to improve diagnosis and risk stratification in patients with chest pain and possible ACS, the use of rest myocardial perfusion imaging has been assigned a class I, level A, indication by the American College of Cardiology/American Heart Association/American Society of Nuclear Cardiology (ACC/AHA/ASNC) Radionuclide Imaging Guidelines for the assessment of myocardial risk in possible ACS patients with a nondiagnostic ECG and initial normal serum markers and enzymes [18].

A possible future approach for risk stratification of patients with suspected ACS involves imaging myocardial fatty acid metabolism. Fatty acid imaging with radioiodine-labeled fatty acid analogs such as ^{123}I-b-methyliodopentadecanoic acid (^{123}I-BMIPP) using SPECT is still an investigational area for the assessment of ischemic memory. After an ischemic episode, abnormalities in fatty acid metabolism may persist long after perfusion has returned to normal, a finding termed ''ischemic memory.'' During this time period, the myocardium garners the bulk of its energy from glucose metabolism [6]. Among patients presenting to the emergency department with ACS and no prior myocardial infarction, the clinical utility of ^{123}I-BMIPP for identifying myocardial ischemia was examined in 111 consecutive patients [19]. All patients were admitted and underwent a rest myocardial perfusion SPECT study within 24 h of chest pain, rest ^{123}I-BMIPP metabolic imaging within 48 h after the perfusion SPECT, and coronary angiography within 1–4 days of admission. ^{123}I-BMIPP defects at rest were present in 74% of patients with documented coronary artery stenosis or vasospasm (on ergonovine provocation), whereas only 38% of patients showed myocardial perfusion defects at rest ($P < 0.001$). Both ^{123}I-BMIPP and perfusion studies were normal in nearly 90% of patients without coronary artery stenosis or vasospasm.

Conti et al. evaluated the implementation of exercise MPI in the early triage of 306 patients with suspected ACS and normal findings on an initial workup [20]. The sensitivity and specificity to predict significant CAD or adverse events within 6 months were 94% (45/48) and 77% (198/258), respectively. A large observational study of 805 patients with low to intermediate risk of CAD compared the diagnostic performance of rest MPI with stress MPI. In that study, investigators evaluated the sensitivity and specificity for diagnosing the following events within 30 days of MPI: AMI, revascularization, stenosis of more than 70% on invasive CAG not amenable to revascularization, life-threatening complication, or cardiac death. The sensitivity and specificity of rest MPI, 71% (109/153) and 73% (476/652), respectively, were significantly lower than the sensitivity and specificity of stress MPI, 97% (148/153) and 88% (574/652) [21].

Limitation

Physicians should be aware of possible false negative results of rest images in patients with subsided chest pain or balanced ischemia caused by a three-vessel disease. AMI should be excluded before performing stress MPI by measuring serial cardiac markers or performing rest imaging. This need to exclude AMI results in a longer diagnostic workup [1].

Radionuclide imaging in patients surviving ACS

Among patients with acute coronary syndromes, a major benefit results from the utilization of potent antithrombotic

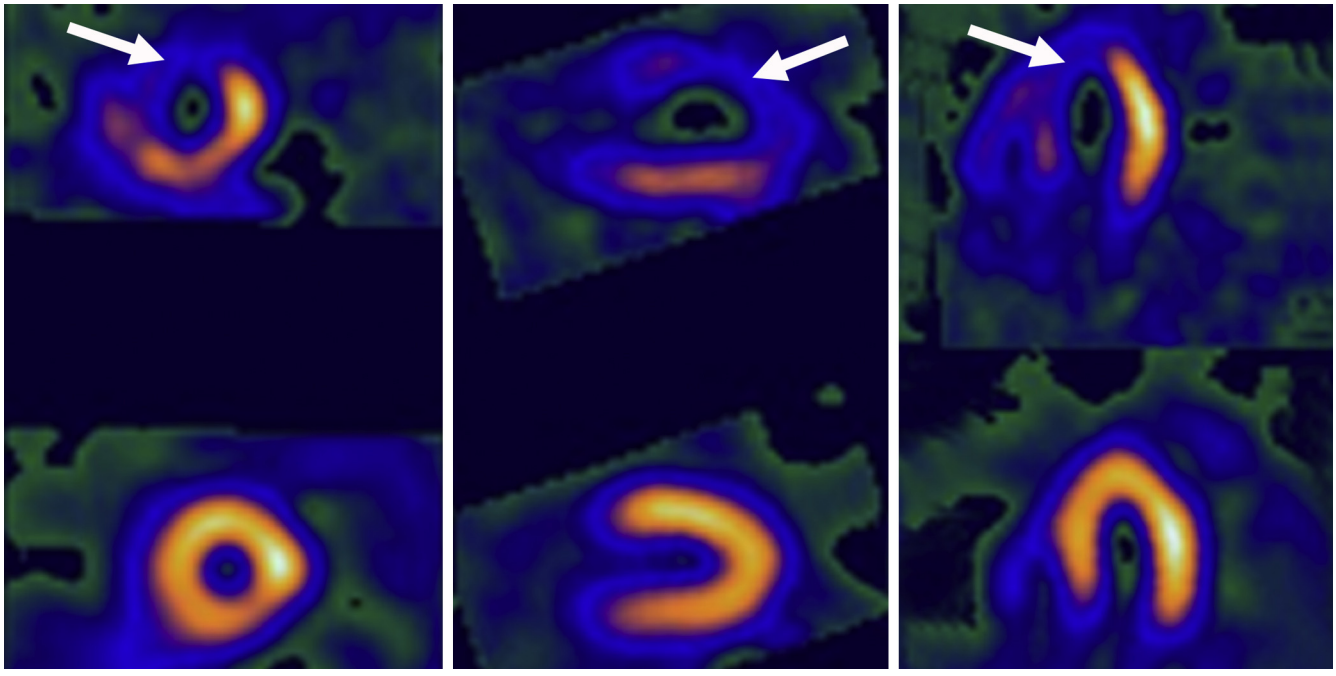

Fig. 1 – Reversible perfusion defect in the area of an anterior wall and a septum of the left ventricle (probably in the territory of the left anterior descending coronary artery). Upper row – stress perfusion, lower row – rest perfusion. Short axis slice on the left, vertical long axis slice in the middle and horizontal long axis slice on the right. Images performed with ^{99m}Tc MIBI using SPECT technique.

regimens and early recanalization of infarct-related artery. Yet, in real life, they still present a 10–15% risk of death at 6 months and an even higher risk of re-infarction and heart failure [9]. It is well established that myocardial function and perfusion represent important determinants of long-term outcome. In this regard, radionuclide imaging is able to evaluate a degree of the left ventricular dysfunction as well as to assess the volume of an infarcted myocardium, jeopardized myocardium by detecting a residual ischemia, and the volume of a viable myocardium [22,23].

Analysis of LV function on gated studies correlated well with MRI in a meta-analysis of nine studies. However, the margin of error was higher in women with smaller left ventricular volumes, with dilated cardiomyopathy and in the presence of global subendocardial perfusion defects [2].

SPECT imaging has been available since the 1970s and has given us a large body of evidence confirming its diagnostic and prognostic value. The commonly used radiopharmaceuticals are thallium-201 chloride and technetium-based agents such as ^{99m}Tc sestamibi and ^{99m}Tc tetrofosmin. Reversible defect, which means reduced tracer uptake on the stress acquisition which disappears on the rest acquisition (Fig. 1), is typical for ischemia (de facto exhausted coronary flow reserve (CFR)). A fixed defect, i.e., a defect present on both stress and rest acquisitions (Fig. 2), is suggestive of a scar or hibernating myocardium provided attenuation artifacts are ruled out. Applying state-of-the-art technology and radiopharmaceuticals, the sensitivity and specificity for detecting occlusive CAD with gated SPECT are now in the range of 91% and 72%, respectively [6]. PET imparts a higher specificity than SPECT, around 90%, which is most likely a consequence of its superior attenuation correction, increased count-density images, and superior spatial resolution. In a meta-analysis of 19 studies, PET had a sensitivity of 92% and a specificity of 85% for diagnosing significant CAD (defined as >50% luminal narrowing) [24]. Moreover, PET has the advantage of being able to measure myocardial blood flow in absolute units, which is important in the assessment of the distal coronary microcirculation [25,26]. Dynamic PET imaging, with the utilization of appropriate tracers and kinetic models, allows regional measurement of absolute MBF, expressed as milliliters per minute per gram. Moreover, the measurement of MBF at rest and during maximal hyperemia, obtained by systemic infusion of adenosine or dypiridamole, allows to quantify CFR, defined as the ratio of MBF at maximal coronary vasodilation to that at rest. CFR represents an integrated measure of blood flow through all coronary arterial bed since an abnormal CFR can be either related to a narrowing of an epicardial coronary artery or reflect coronary microvascular dysfunction [27,28]. A false negative study using SPECT may be a feature of three-vessel and left main stem disease because SPECT assesses relative perfusion. Normal perfusion is seen in up to 13–15% of patients with left main stem disease on account of balanced ischemia in multivessel disease [29]. False positive tests due to attenuation artifacts lower the specificity. For example, an elevated diaphragm results in an apparent fixed defect in the inferior wall in men, and breast artifact gives rise to an apparent defect in the anterior wall in women. Implementing gated studies, attenuation correction algorithm and prone imaging help improve the specificity by reducing the number of equivocal scans in such cases. Referral bias, introduced by the fact that only patients with a positive test will undergo an invasive angiogram, also falsely lowers the specificity.

Viability assessment is usually based on demonstration of the integrity of the cell membrane and the presence of residual perfusion following an injection of a perfusion tracer [2,30]. Pooled meta-analysis of thallium and tetrofosmin studies

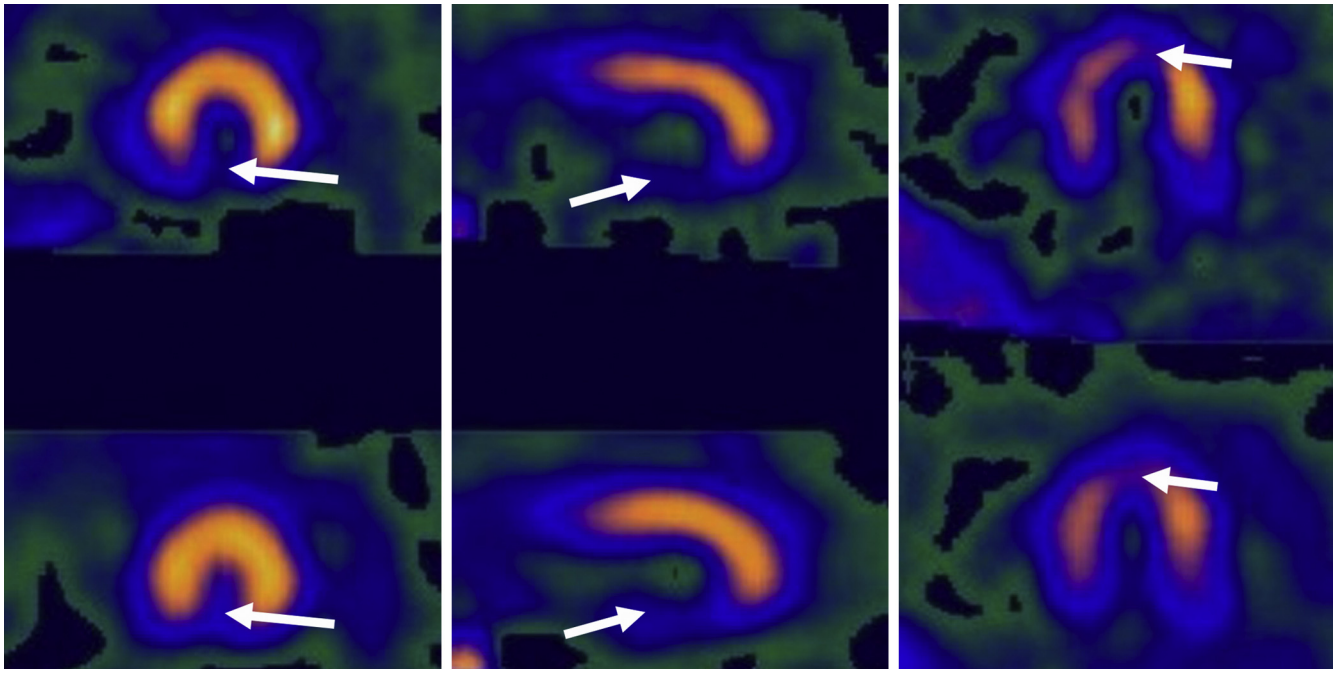

Fig. 2 – Fixed perfusion defect in the area of inferior wall of the left ventricle (probably in the territory of the right coronary artery). Arrangement of the images as in Fig. 1. Images performed with ^{99m}Tc MIBI using SPECT technique.

suggests good sensitivity of 83–88% and a modest specificity of 49–69% for prediction of regional functional recovery after revascularization. This suggests that it has a good negative predictive value. The poor positive predictive value is due to the poor spatial resolution of the technique. Subendocardial infarcts are beyond the spatial resolution of SPECT and are likely to be missed, leading to overestimation of viability.

^{18}F-FDG is the most utilized metabolic tracer to study carbohydrate metabolism and, since cellular glucose uptake is proportional to its consumption, the measurement of ^{18}F-FDG uptake, expressed as micromoles per minute per gram, provides an indirect quantification of its effective utilization [9]. Under ischemic conditions, the reduction of oxygen supply is associated with a decrease in FFA oxidative metabolism and a switch to preferential glucose utilization for myocardial energy production. However, due to high inter-individual variability and low normal glucose cardiac utilization, accurate quantification of myocardial ^{18}F-FDG uptake requires steady state and standardized metabolic conditions that can be achieved by a hyperinsulinemic-euglycemic clamp. This protocol is based on concomitant administration of intravenous glucose load and insulin, leading to a switch of myocardium metabolism to glucose and maximizing ^{18}F-FDG uptake, thus optimizing image quality. During a hyperinsulinemic-euglycemic clamp, absolute regional myocardial ^{18}F-FDG uptake can be reliably quantified.

In the setting of chronic CAD, the concomitant assessment of myocardial perfusion and metabolism allows an accurate differentiation between hibernated and infarcted myocardium in regions characterized by severe contractile impairment. In the presence of ''perfusion–metabolism match'' (Fig. 3), a severely reduced or absent glucose metabolism indicates scar tissue unlikely to recover upon reperfusion. Conversely, in the presence of ''perfusion–metabolism mismatch'' (Fig. 4), preserved or even enhanced glucose metabolism indicates hibernating myocardium susceptible of functional recovery upon reperfusion. The applicability of a perfusion/metabolism match/mismatch model, however, is controversial in the sub-acute phase of STEMI, due to the complex mechanisms of myocardial response to necrosis involving coronary microcirculation dysfunction and tissue inflammation [9]. Because of these complexities, a ''mismatch pattern'' in the sub-acute phase of STEMI can be caused by epicardial artery occlusion, coronary microvascular obstruction, inflammatory cell activation, or a combination of these mechanisms. So the study of myocardial perfusion and metabolism by PET in the sub-acute phase of STEMI has allowed us to considerably improve our knowledge of its pathophysiology, but its clinical usefulness is limited by the complex interplay between epicardial artery obstruction, coronary microvascular obstruction, and inflammatory cell activation. On the other hand the assessment of myocardial perfusion using ammonia labeled with ^{13}N could predict functional recovery after an AMI. Lancellotti et al. have demonstrated that regions with an ammonia uptake of >63% of maximal segment uptake as compared with that observed in normal subjects showed a significant improvement in wall

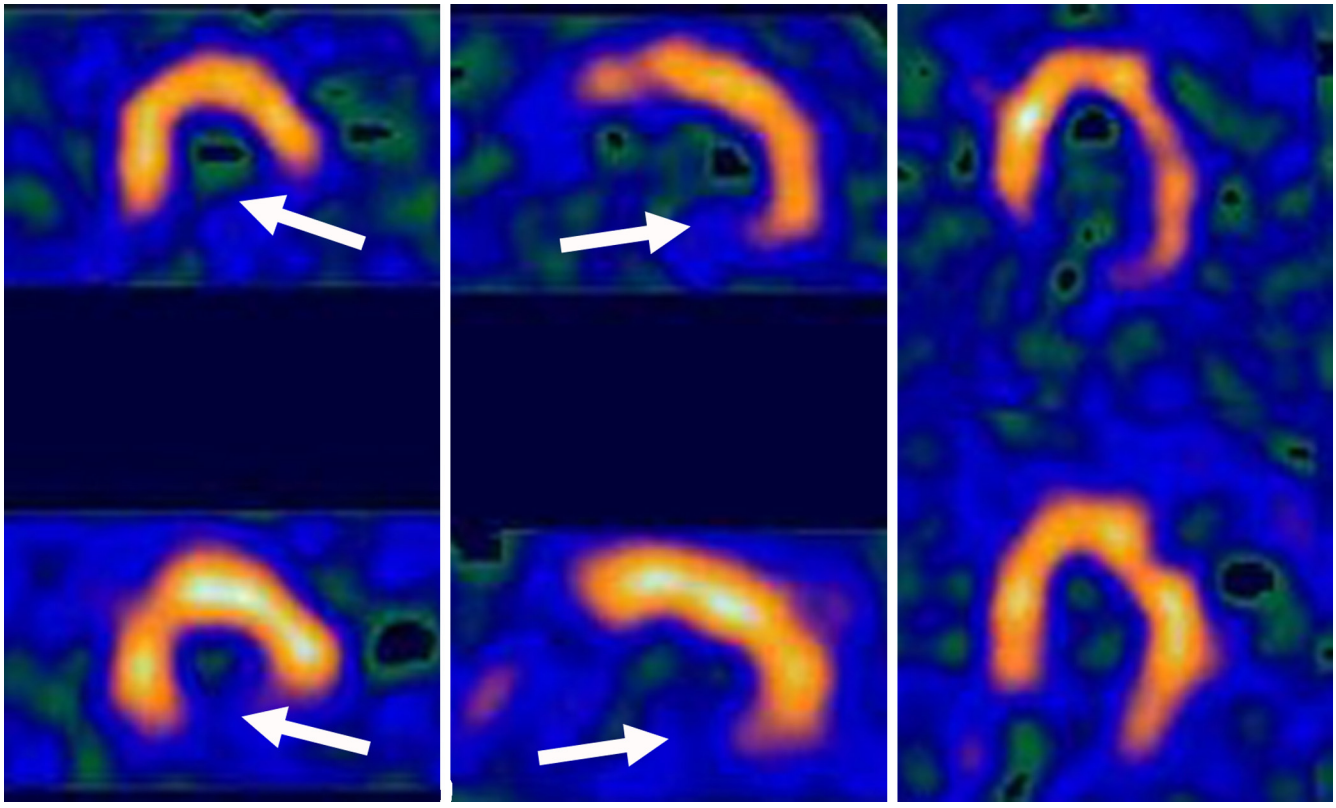

Fig. 3 – Perfusion–metabolism match: scar tissue in the area of inferior wall (probably in the territory of the right coronary artery). Upper row – perfusion (^{99m}Tc MIBI), lower row – glucose metabolism (^{18}F-FDG). Arrangement of the images as in Fig. 1. Images performed with simultaneous acquisition using SPECT technique.

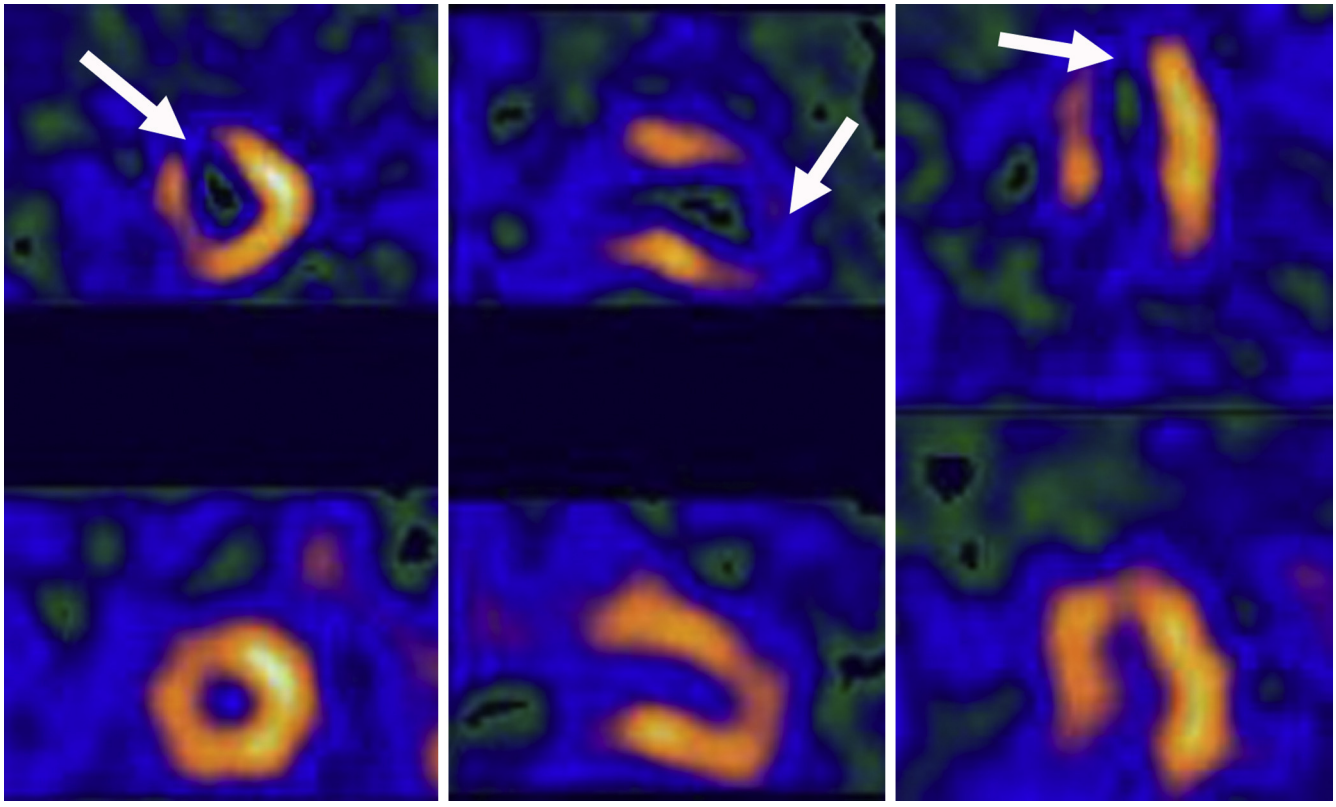

Fig. 4 – Perfusion–metabolism mismatch: viable hibernating myocardium in the area of the apex and the surrounding tissue of the left ventricle. Arrangement and imaging as in Fig. 3.

motion with a predictive value of 86%, while a limited accuracy was found for segments with moderately (between 63% and 50%) and severely (<50%) reduced flow [31].

Conclusion

There are no significant differences among radionuclide imaging, CT angiography and echocardiography for the detection of both ACS and CAD with or without follow-up [1]. It is important to keep in mind that the optimal imaging strategy is determined not only by the diagnostic performance of a modality but also by local practice, expertise with imaging techniques, medical facilities, and individual patient characteristics. Given the absence of large differences in diagnostic performance, these practical aspects may be even more important.

Conflict of interest

The author works as a physician in the department of nuclear medicine.

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Ethical statement

The research was done according to the ethical standards.

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